Laboratory Animal Medicine

EDITED BY

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Preface

The American College of Laboratory Animal Medicine (ACLAM) was founded in 1957 to encourage education, training, and research in laboratory animal medicine and to recognize veterinary medical specialists in the field by certification and other means. Continuing education has been an important activity in ACLAM from its inception. This teaching text, "Laboratory Animal Medicine," reflects the College's continuing effort to foster education. It is, in part, a distillation for teaching purposes of a series of volumes on laboratory animals developed by ACLAM over the past decade: "The Biology of the Laboratory Rabbit" published in 1974, "The Biology of the Guinea Pig" in 1976, and a two-volume work "Biology of the Laboratory Rat" in 1979 and 1980. Also, in 1979 the college published a two-volume text on "Spontaneous Animal Models of Human Disease." In 1981–1983, four volumes of "The Mouse in Biomedical Research" were published.

Most major advances in biology and medicine in one way or another have depended on the study of animals. During the past generation, the health, genetic integrity, and environmental surroundings of the animals have been recognized as important factors to be taken into account in planning animal studies. The ultimate responsibility for insuring the validity of scientific results, together with humane and scientifically appropriate animal care, resides with two categories of scientists: veterinarians responsible for the acquisition, care, nutrition, anesthesia, and other aspects of humane animal use and scientific investigators who use animals as subjects of study. This book therefore is intended for students of veterinary medicine and others in the fields of biology and medicine who utilize animals in biomedical research. The editors and contributors hope it will prove useful in introducing students to important concepts related to animals in research.

The contents of this book are presented in twenty-six chapters that provide information on the diseases and biology of the major species of laboratory animals used in biomedical research. The history of laboratory animal medicine, legislation affecting laboratory animals, experimental methods and techniques, design and management of animal facilities, zoonoses, biohazards, animal models, and genetic monitoring are also covered. The editors acknowledge the contributors' outstanding efforts to follow the guidelines on content and accept sole responsibility for any significant omissions.

As with all volumes of the ACLAM series texts, the contributors and editors of this book have donated publication royalties to the American College of Laboratory Animal Medicine to foster continuing education in laboratory animal science. It could not have been completed without the support and resources of the editors' parent institutions. A special thanks also is extended to the reviewers of each chapter whose excellent and thoughtful suggestions helped the authors and editors present the material in a meaningful and concise manner. We acknowledge and thank Rosanne Brown and Kathi Edelson for their secretarial assistance. The assistance of the staff of Academic Press also is greatly appreciated and acknowledged.

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Contents

Chapter 1

Laboratory Animal Medicine: Historical Perspectives

Bennett J. Cohen and Franklin M. Loew

I. INTRODUCTION

Five key terms identify the fields or activities that relate to the care and use of animals in research, education, and testing. *Animal experimentation* refers to the scientific study of animals, usually in a laboratory, for the purpose of gaining new biological knowledge or solving specific medical, veterinary medical, dental, or biological problems. Most commonly, such experimentation is carried out by or under the direction of persons holding research or professional degrees (e.g., Ph.D., D.D.S., D.V.M., M.D.). *Laboratory animal care* is the application of veterinary medicine and animal science to the acquisition of laboratory animals and to their management, nutrition, breeding, and diseases. The term also relates to the care that is provided to animals as an aid in managing injury and pain. Laboratory animal care usually is provided in scientific institutions under veterinary supervision or guidance. *Laboratory animal medicine* is recognized by the American Veterinary Medical Association as the specialty field within veterinary medicine that is concerned with the diagnosis, treatment, and prevention of diseases in animals used as subjects in biomedical activities. Laboratory animal medicine also encom-

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passes the methods of minimizing pain or discomfort in research animals and the identification of complicating factors in animal research. *Comparative medicine* is "the study of the nature, cause and cure of abnormal structure and function in people, animals and plants for the eventual application to and benefit of all living things" (Bustad *et al.*, 1976). *Laboratory animal science* is the body of scientific and technical information, knowledge, and skills that bears on both laboratory animal care and laboratory animal medicine and that is roughly analogous to "animal science" in the agricultural sector.

Laboratory animal medicine has grown rapidly because of its inherent scientific importance and because good science and the public interest require the best possible care for laboratory animals. In this chapter, we trace briefly the historical evolution of laboratory animal medicine and consider its relationship to other areas of biology and medicine.

II. ORIGINS OF ANIMAL EXPERIMENTATION

The earliest references to animal experimentation are to be found in the writings of Greek philosopher–physicians of the fourth and third centuries BC. Aristotle (384–322 BC), characterized as the founder of biology, was the first to have made dissections which revealed internal differences among animals (Wood, 1931). Erasistratus (304–258 BC) probably was the first to perform experiments on living animals, as we understand them today. He established in pigs that the trachea was an air tube and the lungs were pneumatic organs (Fisher, 1881). Later, Galen (130–200 AD) performed anatomical dissections of pigs, monkeys, and many other species (Cohen and Drabkin, 1948; Cohen, 1959a). Galen justified experimentation as a long arduous path to the truth, believing that uncontrolled assertion that was not based on experimentation could not lead to scientific progress. Dogma replaced experimentation in the dark centuries following Galen's lifetime. Whereas anatomical dissection of dead animals and people had been among the earliest types of experimentation, in medieval times this was prohibited by ecclesiastical authorities who wanted to prevent acquisition of knowledge about the natural world that could be considered blasphemous. Not until the 1500s was there a reawakening of interest in science. Andreas Vesalius (1514–1564), the founder of modern anatomy, used dogs and pigs in public anatomical demonstrations (Saunders and O'Malley, 1950) (Fig. 1). This "vivisection" led to great leaps in understanding of anatomy's correspondence with physiology. In 1628, Sir William Harvey published his great work on the movement of the heart and blood in animals (Singer, 1957). By the early 1700s, Stephen Hales, an English clergyman, reported the first measurement of blood pressure, using as his subject a horse "fourteen hands high, and about fourteen years of age, (and with) a fistula on her withers. . . ." (Hoff *et al.*, 1965) (Fig. 2). During the 1800s France became a primary center of experimental biology and medicine. Scientists, such as François Magendie (1783–1855) and Claude Bernard (1813–1878) (Fig. 3) in experimental physiology and Louis Pasteur (1827–1895) in microbiology, contributed enormously to the validation of the scientific method which included the use of animals. Bernard (1865) commented:

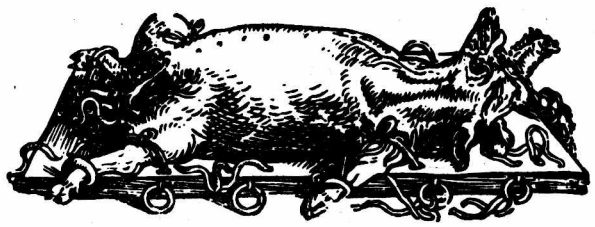

Fig. 1. Illustration by Andreas Vesalius. Pig tied to dissection board "for the administration of vivisections." (From Saunders and O'Malley, 1950.)

> . . . it is proper to choose certain animals which offer favorable anatomical arrangements or special susceptibility to certain influences. For each kind of investigation we shall be careful to point out the proper choice of animals. This is so important that the solution of a physiological or pathological problem often depends solely on the appropriate choice of the animal for the experiment so as to make the result clear and searching.

Pasteur studied infectious diseases in a variety of animals, such as silkworms ("pebrine"), dogs (rabies), and sheep (anthrax). "Pebrine" (pepper) was an economically important disease of silkworms in France when silk was a major fabric; Pasteur and others demonstrated the parasite which caused the disease Duclaux, 1920). As pathogenic organisms were identified that could be related to specific human diseases, their animal disease counterparts also were studied. Pasteur and others perceived that the study of animal diseases benefited animals and enhanced understanding of human diseases and pathology. The extraordinary power of the experimental approach, including experiments on animals, led to what has been called the Golden Age of scientific medicine. Despite advances in physiological and bacteriological understanding, however, criticisms of the use of animals in science began, particularly in England (Loew, 1982). The first Society for the Prevention of Cruelty to Animals (SPCA) was established in England, followed in the 1860s by an American SPCA in New York, a Philadelphia SPCA, and a Massachusetts SPCA. Objections to the use of animals in science were part of the concerns of these societies, particularly since Darwin's findings on evolution made "differences" between animals and men less sure in many persons' minds (Loew, 1982).

Most American and Canadian scientists, physicians, and vet-

Statical ESSAYS:
CONTAINING
HÆMASTATICS;
Or, An Account of ſome
Hydraulic and *Hydroſtatical*
EXPERIMENTS
MADE ON THE
Blood *and* Blood-Veſſels *of* ANIMALS.
ALSO
An Account of ſome EXPERIMENTS on Stones in the *Kidneys* and *Bladder*; with an Enquiry into the NATURE of thoſe *anomalous* Concretions.
To which is added,
An *APPENDIX*,
CONTAINING
OBSERVATIONS and EXPERIMENTS relating to ſeveral Subjects in *The Firſt Volume*. The greateſt Part of which were read at ſeveral *Meetings* before the Royal Society.
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Fig. 2. Title page from "Statical Essays" (Hales, 1740).

erinarians soon applied emerging scientific concepts in their research. D. E. Salmon, recipient of the first D.V.M. degree awarded in the United States (by Cornell University in 1879), studied bacterial diseases, and the genus *Salmonella*, a ubiquitous human and animal pathogen, was named for him. Cooper Curtice (Fig. 4), Theobald Smith, and others first demonstrated the role of arthropod victors in disease transmission in their studies of bovine Texas fever (Schwabe, 1978). The first paper published at the then-fledging Johns Hopkins Hospital and School of Medicine was by the physician William H. Welch, for whom *Clostridium welchii* was named and was entitled "Preliminary Report of Investigations concerning the Causation of Hog Cholera" (Welch, 1889). Thus, it became evident that the study of the naturally occurring diseases of animals could illuminate principles applicable to both animals and mankind and lead to improved understanding of biology in general.

John Call Dalton, M.D. (1825–1889), an American physiologist, spent a year in Bernard's laboratory in Paris, about 1850. He was highly impressed with Bernard's instructional methods, which included demonstrations in living animals of important physiological principles. Subsequently, Dr. Dalton included such demonstrations in his teaching at the College of Physicians and Surgeons in New York City (Mitchell, 1895), the forerunner of the "animal labs" in which generations of students in biology and medicine have been trained. When Alexis Carrel received the Nobel Prize in 1912, the citation stated in part (Malinin, 1979): ". . . you have . . . proved once again that the development of an applied science of surgery follows the lessons learned from animal experimentation." Thus, starting in ancient times and continuing to the present day, animal experimentation has been one of the fundamental approaches of the scientific method in biological and medical research and education.

Fig. 3. Claude Bernard, often referred to as the founder of experimental medicine, developed and described highly sophisticated methods of animal research in his laboratory in Paris. (Photograph from Garrison, 1929.)

Fig. 4. Dr. Cooper Curtice examining ticks on a cow dead of Texas fever. Curtice contributed importantly to the demonstration that arthropods can act as carriers of mammalian diseases. (Courtesy of *The Nation's Business.*)

III. EARLY VETERINARIANS IN LABORATORY ANIMAL SCIENCE AND MEDICINE

On September 15, 1915 Dr. Simon D. Brimhall (1863–1941, V.M.D., University of Pennsylvania, 1889) (Fig. 5) joined the staff of the Mayo Clinic in Rochester, Minnesota, the first veterinarian to fill a position in laboratory animal medicine at an American medical research institution (Cohen, 1959b; Physicians of the Mayo Clinic and the Mayo Foundation, 1937). There was no such recognized field at the time, of course; but Dr. Brimhall's activities—management of the animal facilities, development of animal breeding colonies, investigation of laboratory animal diseases (Brimhall and Mann, 1917; Brimhall and Hardenbergh, 1922), and participation in collaborative and independent research (Brimhall *et al.*, 1919–1920)—were the prototype of the present role of "laboratory animal veterinarians" in scientific institutions throughout the world.

The decision to employ a veterinarian at the Mayo Clinic in 1915 appears to have resulted from a unique juxtaposition of institutional needs and personalities. Although the Mayo Clinic was already world renowned, organized research was only in a rudimentary stage of development. About 1910, there was an unsuccessful effort to convert an old barn, belonging to the Chief of Surgical Pathology, Dr. Louis B. Wilson, for animal experimentation (Braasch, 1969). Then, in 1914, with Dr. William J. Mayo's active encouragement, a Division of Experimental Surgery and Pathology was created, the first real research laboratory at the Clinic. Dr. Frank C. Mann, a young medical scientist from Indiana, was invited to head the Division, with the primary assignment of developing a first class animal research laboratory. Dr. Brimhall's employment followed within a year and was accompanied by the planning and ultimate construction of new animal facilities (Figs. 6 and 7). Christopher Graham, M.D., then head of the Division of Medicine, greatly influenced the decision to employ Dr. Brimhall. Perhaps the fact that Dr. Graham also was a veterinarian (V.M.D., University of Pennsylvania, 1892) provided insights into the contributions that veterinary medicine could make to experimental surgery and pathology. Certainly, the concept of mutual support among the professions was not at that time widely held; there was, in fact, relatively little interprofessional communication between medicine and veterinary medicine then.

Dr. Brimhall retired in 1922 and was succeeded by Dr. John G. Hardenbergh (1892–1963; V.M.D., University of Pennsyl-

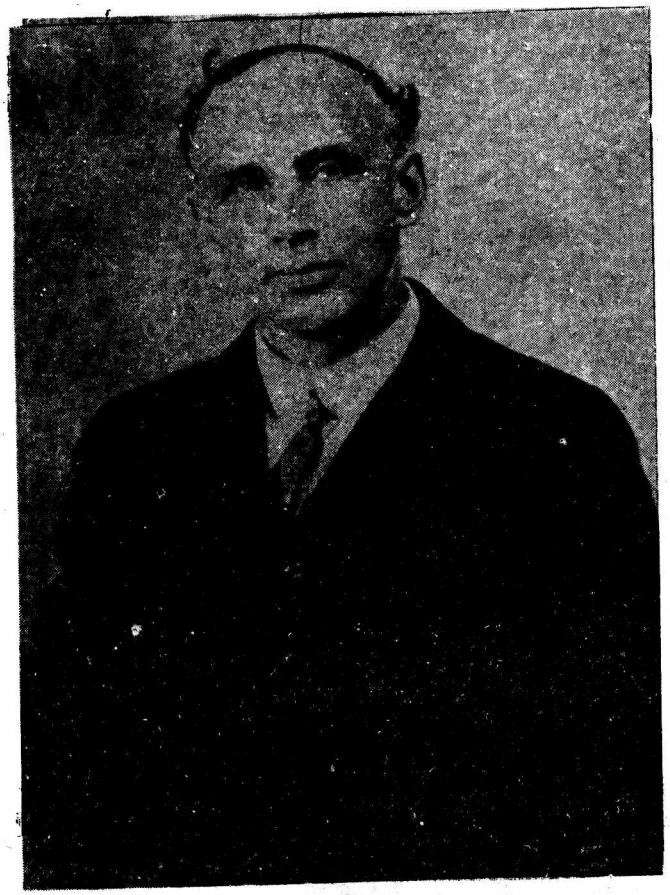

Fig. 5. Simon D. Brimhall, V.M.D., the first veterinarian in laboratory animal medicine at an American medical research institution, worked at the Mayo Clinic from 1915 to 1922. (Courtesy of University of Minnesota Press and Dr. Paul E. Zollman.)

vania, 1916). During his 5-year tenure at the Mayo Clinic, Dr. Hardenbergh was an active clinical investigator (Hardenbergh, 1926–1927) as well as animal facility manager. In a stout defense of animal experimentation, he also demonstrated the communication skills in the public arena that were to serve him well later in his career (1941–1958) as Executive Secretary of the American Veterinary Medical Association (Hardenbergh, 1923).

Dr. Carl F. Schlotthauer (1893–1959, D.V.M., St. Joseph Veterinary College, 1923), who had joined the Mayo Clinic staff in 1924 as assistant in veterinary medicine, succeeded Dr. Hardenbergh in 1927. By this time, the Mayo Foundation was functioning as the graduate medical education and research arm of the Mayo Clinic, and had become formally affiliated with the University of Minnesota. Dr. Schlotthauer ultimately (1952) became head of the Section of Veterinary Medicine at the Mayo Foundation and Professor of Veterinary Medicine at the University of Minnesota Graduate School (1945). Thus, Dr. Schlotthauer was the first veterinarian to attain a full professorship for laboratory animal medicine–related academic activities. Dr. Schlotthauer vigorously opposed antivivisectionist attacks on animal research. He was a leader in the statewide campaign that led to adoption of the Minnesota "pound law" in 1950, i.e., a law authorizing the requisitioning for research and education by approved scientific institutions of impounded, but unclaimed dogs and cats. Dr. Schlotthauer believed that open and honest communication between medical scientists and humane society workers could lead to better public understanding and support of animal research. Consequently, he was also active in humane society activities, serving, for many years, on the Board of Directors of the Minnesota Society for the Prevention of Cruelty to Animals. Dr. Schlotthauer also was an important figure in the early years of the American Association for Laboratory Animal Science (AALAS). He was a founding member of the Board of Directors and presented a paper on animal procurement at the first meeting in 1950 (Schlotthauer, 1950).

While other veterinarians also held appointments at the Mayo Foundation between 1915 and 1950, Dr. Brimhall, Dr. Hardenbergh, and Dr. Schlotthauer were the ones most closely associated with activities that today are identified with laboratory animal medicine. It is noteworthy that the Mayo Clinic/Foundation has maintained a program in animal medicine continuously for more than 65 years, having initiated it long before most medical research institutions were prepared even to consider the possible value of adding veterinarians to their professional staff (P. E. Zollman, personal communication, 1982).

Karl F. Meyer [1884–1974; D.V.M., University of Zurich, 1924, M.D. (honorary), College of Medical Evangelists, 1936] was an internationally known epidemiologist, bacteriologist and pathologist. Dr. Meyer was intensely interested in matters related to laboratory animals for most of his professional life. He was the author of an early review of laboratory animal diseases (Meyer, 1928), one of the first publications of its kind in the United States. Dr. Meyer was a unique personality—vigorous, dynamic, active—a world traveler on missions related to international health; a scientist who engendered in his students respect, admiration, love, and fear in varying proportions. Together with his long-time associate Bernice Eddy (Ph.D.), a bacteriologist, Dr. Meyer developed a model animal facility at the George Williams Hooper Foundation at the University of California, San Francisco during a 30-year tenure as director (1924–1954). Dr. Meyer often was away from the laboratory, and it fell to Dr. Eddy to supervise the animal facility, which she did with great skill and dedication. Dr. Meyer foresaw the need for and was an early advocate of the participation of veterinarians in the operation of institutional laboratory animal colonies (Meyer, 1958). He figured importantly in the planning that led the Univeristy of Cal-

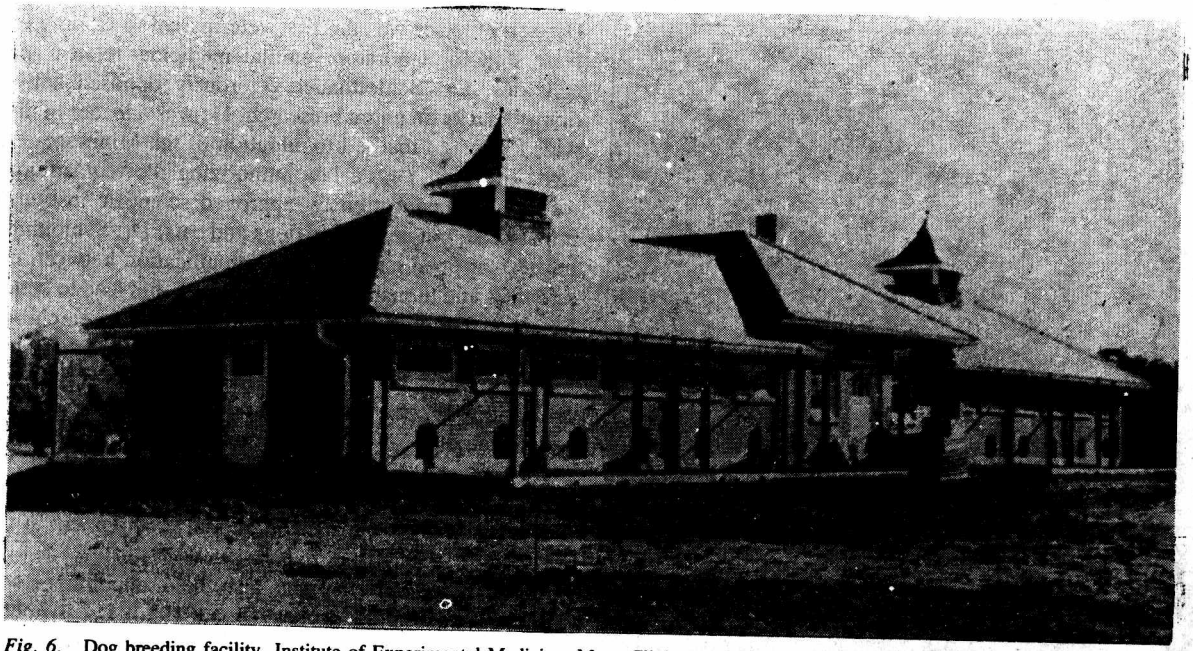

Fig. 6. Dog breeding facility, Institute of Experimental Medicine, Mayo Clinic, constructed mid-1920s. (Courtesy of Dr. Paul E. Zollman.)

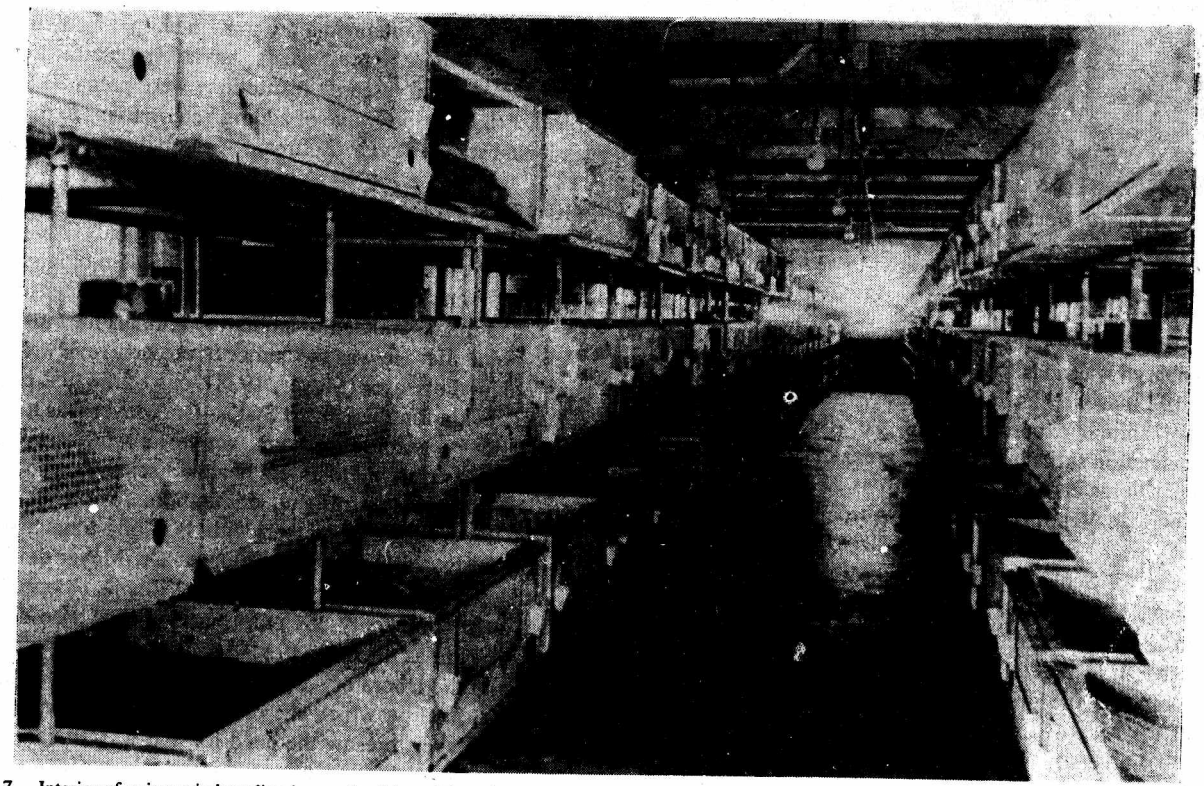

Fig. 7. Interior of guinea pig breeding house, Institute of Experimental Medicine, Mayo Clinic, constructed early 1920s. (Courtesy of Dr. Paul E. Zollman.)